REMARKS

Further and favorable reconsideration is respectfully requested in view of the following comments.

Upon entry of these amendments, claims 1-4, 6-7 and 14-16, as amended, and new claim 17, will be pending.

Claim 1 is amended in consideration of the Examiner's suggestions in the Office Action. Specifically, the amended claim recites "metering in partially the 6-APA and/or ... ." The amended claim also recites, "with a phenylglycine derivative and an enzyme to provide a reaction mixture."

The Examiner has also questioned how "batch" defines the process. It is respectfully submitted, however, that those skilled in the art understand the meaning of a "batch" reaction as compared, for example, to a "continuous" reaction. However, since "batch" is not required to distinguish over the prior art, this term is deleted from the preamble of claim 1.

The language "maintaining the total concentration in the reaction mixture" has been removed from the claims and the language formerly used in claim 1 is re-inserted, noting that there were no formal rejections applied to this earlier version of the claims.

The question of "how one can measure the 'total concentration' of 6-APA and amicillin (sic) in the reaction mixture when the whole purpose is to produce amicillin (sic)" is not particularly understood. In any event, a similarly presented question in the Office Action dated November 23, 2001, was responded to and repeated herein.

Since product may be formed throughout the course of the reaction its concentration may change throughout the reaction. Similarly, the amount of reactant, being consumed and/or added during the course of the reaction, may change throughout the course of the reaction. Nevertheless, this does not preclude taking a sample at any particular time and measuring the amount of 6-APA and ampicillin in the reaction mixture. This is precisely what is shown in the graphs appended to the application. Techniques for measuring concentrations of 6-APA and ampicillin are well known in the art, for example, as shown in WO '061.

It should be noted that claims with substantially the same language as now presented were not considered to be indefinite.

The Examiner has also questioned the phrase "and or" in "step" ii), however, Applicants' version of the pending claim 1 does not show "and or" in ii) but shows "and/or" as suggested by the Examiner. The "and/or" terminology is present in the claims filed herewith.

For "step" iii) substantially the same change as presented for "step" i) is again presented.

With regard to the question "at what point in the reaction does the acylation occur" it is noted that ii) now recites "in the course of the enzymatic acylation reaction" which is consistent with the language of, for example, original claim 5. The terminology "acylation reaction" is now used throughout the claims for consistency.

With respect to the suggestion that claim 1 should recite definite "steps" in chronological order, in view of the current amendments it is believed that this suggestion has been addressed.

Accordingly, it is submitted that claim 1, as currently amended, is not indefinite.

Claims 2, 3 and 4 are amended to conform to the language of claim 1, from which they depend. These amendments should address the Examiner's request for further clarity.

Claim 8 is cancelled, without prejudice or disclaimer. Accordingly, the Examiner's comment that claim 8 is confusing is moot.

Furthermore, while not agreeing that the language of claim 14 was confusing or that the size of the "portion" as a percentage of the total amount was critical, nevertheless, claim 14 is amended to more positively recite the step of introducing a portion of the total amount of 6-APA at the beginning of the reaction, such that the amount of dissolved 6-APA is less than 300 mM and that the remainder of the total amount is added during the course of the acylation reaction to maintain the amount of dissolved 6-APA lower than 300 mM throughout the reaction. This is consistent with the written description of the invention, *see, e.g.*, page 4, and fully addresses the Examiner's concern regarding claims 14-16.

New claim 17 provides an alternative description of an embodiment of Applicants' invention which also takes into consideration the language which was considered by the Examiner confusing or indefinite. Claim 17 is supported throughout the application as originally filed.

Accordingly, no new matter is added by the claim amendments.

Having addressed the formal issues under 35 U.S.C. 112, it is respectfully submitted that the pending claims are directed to a novel and nonobvious invention.

Accordingly, the rejection of claims 1-4, 6-8, 11 and 14-16, as *prima facie* obvious, under 35 USC §103, in view of WO 92/01061 (WO '061) taken with WO 95/03420 (WO '420), is respectfully traversed.

The pending claims are patentable, at least for the reason that the cited prior art does not even remotely disclose or suggest metering either or both of the 6-APA or phenylglycine derivative to the reaction mixture. The practitioner of ordinary skill would not have been motivated to carry out the enzymatic acylation reaction under these conditions because the cited references do not suggest that metering would be effective to maintaining the concentration of 6-APA at lower than 300 mM or that maintaining the concentration of 6-APA in the reaction media at any particular concentration, including a concentration lower than 300 mM or 250 mM, would have a beneficial effect on the outcome of the reaction.

It is, however, the Examiner's position that

> "[t]o add slowly and in a meticulous manner as in metering is well known in the art and is fully contemplated by the references. One of ordinary skill in the art reading the references would have fully realized that adding in the ingredients slowly in a meticulous fashion would work well. It is simply the choice of the artisan in an effort to optimize the results to add the ingredients in such a fashion. In fact, one would be motivated to do so since adding the ingredients in slowly gives them ample time to react properly with one another and produce a better yield of product."

Applicants respectfully disagree for several reasons.

Initially, it is respectfully submitted that the Examiner is attempting to introduce limitations into the claims which are not required by the claim language or

intent. The claims do not address the rate of addition, for example, "slowly" or "meticulously." Thus, it is within the scope of the claims to add, including rapidly, all of the 6-APA or the phenylglycine derivative at the beginning of the process to the reaction mixture, as long as the fed (or metered) amount added does not cause, for example, the concentration of dissolved 6-APA or the total concentration in the reaction mixture of 6-APA and ampicillin to exceed or fall below the desired amount

This is certainly not addressed or suggested in the cited references.

The suggestion of what the artisan would have realized is mere speculation without basis in fact found in the reference's disclosures.

According to WO '061 it is expressly disclosed that all of the acylating agent is added to provide a minimum initial concentration in the reaction mixture. However, whether added in portions or all at once, there is no disclosure or suggestion in the art that adding the reactants under conditions which provides a relatively low concentration of dissolved 6-APA (lower than 300 mM), while maintaining at least a minimum total concentration of 6-APA and ampicillin (greater than 250 mM), or which provides a molar ratio of the total quantity of acylating agent to the total quantity of 6-APA would have any effect, much less a beneficial effect, on the outcome of the reaction.

More particularly, the disclosure on page 5 of WO '061 is that the process is characterized by the concentration of the starting amino β-lactam in the reaction mixture and, in this respect, the preference is clearly to the higher end of the concentration range. Under these conditions, therefore, it is respectfully submitted that the practitioner would not have been motivated to "optimize" the reaction by adding the 6-APA and/or phenylglycine derivative under conditions which would take into consideration the amount of dissolved 6-APA, which amount is not at all addressed in the art.

As explained in *In re Freed*, 425 F.2d 785, 165 USPQ 570 (CCPA 1970) a reference that teaches a chemical process would logically and reasonably be inferred as setting out the least number of reactions thought necessary to accomplish the desired objective. Thus, one skilled in the art would logically and reasonably presume

that if the reactants were not combined in the manner disclosed in the reference, some adverse side effect or no reaction at all would occur.

Accordingly, in a manner analogous to the number of reaction steps, in this case, it is logical and reasonable to assume that the manner of combining the reactants disclosed in WO '061 would necessarily be construed by the practitioner as being required to practice the chemical process there described.

In addition, and as noted above, WO '061 does not describe a solution concentration, i.e., dissolved amount, of 6-APA, lower than 300 mM. Similarly, WO '420, does not describe the dissolved concentration of 6-APA being lower than 300 mM. Accordingly, the combined disclosures of the references must also fail to disclose at least this feature of the present invention.

Therefore, no proper case of *prima facie* obviousness has been established in the record. Accordingly, Applicants request withdrawal of this rejection based on the disclosures of WO '061 and WO '420.

While, for the reasons given above, the pending claims are believed to be directed to allowable subject matter, it is further submitted that the process as claimed provides unexpectedly superior results which are neither suggested nor obvious over the prior art of record.

The objective of WO '061 is to obtain high conversion with respect to 6-APA. This high conversion is, however, accomplished only at the expense of low conversion of the acylating agent (phenylglycine derivative). Such low conversion is a disadvantage since large amounts of reactants need to be recovered and/or are lost.

Operating under the conditions disclosed in this reference, both high conversion of phenylglycine (PG) derivative and high conversion with respect to 6-APA are not achieved.

More particularly, from the examples in WO '061 which are related to production of ampicillin (as shown in the following table) the conversion with respect to 6-APA varies between 60% and 98% and the conversion with respect to PG derivative varies between 11% and 34%.

Table: examples of WO'61 relating to the preparation of ampicillin (AMP)

Example	Initial conc. 6-APA	Initial conc. PG Deriv.	Ratio k	Total conc. 6-APA+AMP	Conversion of 6-APA	Conversion of PG Deriv.
	mM	MM		mM	(%)	(%)
1 (1st)	100	270	2.7	<100	74	27
1 (2nd)	100	750	7.5	<100	98	13
3 (pH=3)	250	700	2.8	<250	60	21
3 (pH=6.4)	250	700	2.8	<250	94	34
3 (pH=7.0)	250	700	2.8	<250	93	33
4 (T=10 C)	180	700	3.9	<180	95	24
4 (T=20 C)	180	700	3.9	<180	96	25
4 (T=35 C)	180	700	3.9	<180	60	15
5 (1st)	100	270	2.7	<100	74	27
5 (2nd)	100	750	7.5	<100	86	11
6	150	700	4.7	<150	90	19
7	230	920	4	<230	91	23

As may easily be appreciated from the above table, the ratio k is always greater than 2.5 and the total concentration of 6-APA and PG derivative is always less than 250 mM.

For ease of comparison, the following table summarizes results from the specification of the subject application.

Application

	Added 6-APA	Added PG Deriv.	Ratio k	Total conc. 6-APA+AMP	Conversion of 6-APA	Conversion of PG Deriv.
	Mmol	Mmol		mM	(%)	(%)
Example II	600	1000	1.67	>400	96	58
Exp. A	600	950	1.58	>400	92	58

For clarity, it is explained that "conversion" of 6-APA and of PG derivative, is based on the yield of ampicillin (AMP) relative to the total amounts of 6-APA and PG derivative. Thus, in the case of Example II (page 10) the total amount of 6-APA was 600 mmol and the total amount of PGA was 1000 mmol. Therefore, since 575 mmol of AMP was formed the conversions of 6-APA and PGA, are, respectively, (575/600) X 100 and (575/1000) X 100.

It will be recalled that in Experiment A conditions i) and iii) were both satisfied. A high PG derivative conversion (58%) was achieved, even though condition ii) specifying the low concentration of dissolved 6-APA was not satisfied (during the early part of the experiment the concentration of dissolved 6-APA was higher than 300 mM). This is shown in Graph 2.

When condition ii) (as in Example II) is also satisfied, the conversion for 6-APA increases from 92% to 96% while still maintaining high PG derivative conversion.

These conditions and results are not suggested in the disclosure of WO '061. In fact, considering the results from Example 1 (1^{st}) and Example 1 (2^{nd}) wherein the ratio k increased from 2.7 to 7.5 whereas conversion of 6-APA increased from 74% to 98%, one skilled in the art would expect that at low k values only low 6-APA conversions would be obtained. See also the results from Examples 5 (1^{st}) and (2^{nd}) where similar results were obtained.

As noted from the specification, e.g., page 2, line 23 to page 3, line 2, when working at high total concentration of 6-APA and ampicillin combined and a low molar ratio of the total quantity of added phenylglycine derivative to the total quantity of added 6-APA (below 2.5), the conversions of 6-APA and PG derivative, may be unexpectedly increased. In addition to high conversions of both 6-APA and PG derivative, stirrability of the reaction may also be improved when the conditions ii) is satisfied.

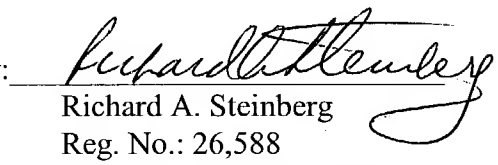
Since there is no suggestion in the disclosure of WO '061 to operate at the conditions specified in the present claims and, certainly, no motivation to operate at a k ratio < 2.5, and at a total concentration of 6-APA and ampicillin greater than 250 mM, much less at the totally undisclosed low concentration of dissolved 6-APA (as opposed to undissolved/solid 6-APA) the present invention, would not have been obvious over the cited references.

In view of the above amendments to the claims and the foregoing remarks, the Applicants respectfully assert that all of the Examiner's objections and rejections have been overcome. Accordingly, early and favorable notice of allowance of the present application with claims 1-4, 6-7, and 14-17, is respectfully requested.

If for any reason the application is not yet in condition for allowance, the Examiner is invited to contact Applicants' undersigned counsel to resolve any remaining issues.

Respectfully submitted,

PILLSBURY WINTHROP, LLP

By: 

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